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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/591,847	01/09/2007	**Kenneth Hofland**	BJS-620-454	3278

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EXAMINER	
KRISHNAN, GANAPATHY	
ART UNIT	**PAPER NUMBER**
1623	

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05/13/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/591,847	HOFLAND ET AL.	
	Examiner	Art Unit	
	Ganapathy Krishnan	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed 2/20/2009 has been received, entered and carefully considered.

The following information provided in the amendment affects the instant application:

1. Claim 5 has been amended.

2. Remarks drawn to rejections under double-patenting, 35 USC 102 and 103.

Claims 1-10 are pending in the case.

The rejection of Claim 5 under 35 U.S.C. 102(b) as being anticipated by Jensen et al (WO 97/25044; cited in Search Report of 9/5/2006) has been overcome in view of amendments.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The rejection of Claim 5 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim12 of U.S. Patent No. 6,265,385 ('385) is being maintained for reasons of record and is reiterated here.

Although the conflicting claims are not identical, they are not patentably distinct from each other because:

Instant Claim 5 is drawn to a combined preparation of a topoisomerase II poison and a bis-dioxypiperazine.

Claim 12 of '385 is drawn to a combination of a topoisomerase II poison and a bis-dioxypiperazine, wherein the active agents are specifc compounds

Claim 12 of '385 differs from the instant claims in that the instant claim recites a general class of compound for the two active agents. However, it would have been obvious to one of ordinary skill in the art at the time the invention was made that the specifc active agents recited in '385 could be successfully employed in the instant preparation.

In determining the differences between the prior art and the claims, the question is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art. "The test for an implicit showing is what the combined teachings, knowledge of one of ordinary skill in the art, and the nature of the problem to be solved as a whole would have suggested to those of ordinary skill in the art." *In re Kotzab*, 217 F.3d 1365, 1370, 55 USPQ2d 1313, 1317 (Fed. Cir.

2000). In the instant case, '385 teaches specifc agents that belong to the general class applicant claims. The use of known members of classes of reagents in preparations taught in the prior art is not seen to render the instantly claimed combination unobvious over the art. Once the general class of agents has been shown to be old, the burden is on the applicant to present reason or authority for believing how the specific form of the compound that belongs to that general class would take part in or affect the basic nature of the product and thus the unobviousness of the method of using it.

Response to Applicants Remarks regarding Double Patenting

Applicants have traversed the rejection arguing that the kit of claim 12 of the '385 patent would not have made obvious the invention of specific separate forms as required by claim 5.

Applicants' arguments are not found to be persuasive. One of ordinary skill in the art knows well that drugs can be administered in different forms and that oral and i.v. forms are two of the very commonly used forms. Irrespective of the form in which the drugs are present it would have still been obvious to one of ordinary skill in the art to make a kit comprising the active agents.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The rejection of Claims 1-4 and 6-10 under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 97/25044; cited in Search Report of 9/5/2006) in view of Palepu et al (US 4,963,551; cited in Search Report of 9/5/2006) is being maintained for reasons of record as reiterated below.

Jensen et al teach a method of treating a CNS tumor in humans via administration of a topoisomerase-II poison and a bis-dioxypiperazine compound (page 38, lines 1-9). The bis-dioxypiperazine compound has structural formula (I) (page 11) and the specific compound used is denoted by the symbol ICRF-187 (same as recited in instant claim 3; page 14, lines 11-20). The topoisomerase poison is etoposide (page 40, lines 5-9). The patient can be treated

simultaneously or with different intervals between the two active agents (page 15, line 24 through page 16, line 24). However, Jensen et al do not teach the use of radiation in their method of treatment.

Palepu et al teach the use of piperidinedione (abbreviated as ADR-529 and also known as ICRF-187) is a cardio protective agent used in antitumor therapy and in addition to being a cardio protective agent also acts as a sensitizer to ionizing radiation (col. 1, lines 27-36).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a topoisomerase II poison like etoposide and a dioxypiperazine like dexrazoxane in a method of treatment of CNS tumor in a subject and also use radiation treatment further as instantly claimed since the use of a combination of the topoisomerase poison and a dioxypiperazine for the same is taught in the prior art and the use of radiation in tumor/cancer treatment is also well known.

One of skill in the art would be motivated to make combined preparations and use the active agents in a method as instantly claimed since a dioxypiperazine like dexrazoxane is known to protect the patient from the toxic effects of the topoisomerase II poison (Jensen, page 3, lines 4-12). This makes possible the use of higher doses of the topoisomerase poison. In addition to this, the dioxypiperazine also acts as a sensitizer to radiation, as taught by Palepu et al. Hence the combined use of the active agents and radiation treatment would have the maximum beneficial effect with reduced side effects.

Response to Applicants Arguments regarding rejection under 35 USC 103

Applicants have traversed the rejection arguing that the rejection is based on a single comment by Palepu that a desirable property of ADR-529 is as a sensitizer to ionizing radiation.

This beneficial activity is neither tested nor verified in Palepu. Such an unsupported statement would not have led one of ordinary skill in the art to believe that the presently claimed invention could be successfully made.

Applicants' Arguments are not found to be persuasive.

Palepu expressly teaches that ADR-529 is a sensitizer to ionizing radiation. His teaching is based on what is known in the art. Palepu need not provide test results to verify the statement, especially for something that is known in the art. This is also known to one of ordinary skill in the art and hence the artisan would be motivated to make the combination of the active agents including radiation treatment. One of ordinary skill in the art would have a reasonable expectation of success that such a combination would have additive effects which would be more beneficial. The instant invention is rendered obvious.

The following rejection is made of record necessitated by amendment is made of record.

Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (WO 97/25044; cited in Search Report of 9/5/2006) in view of Palepu et al (US 4,963,551; cited in Search Report of 9/5/2006).

Jensen et al teach a pharmaceutical kit comprising a dosage unit of a bis-dihydroxypiperazine and a dosage unit of a topoisomerase II poison (a combined preparation; page 44, lines 6-12; page 6, lines 12-20). However, he does not teach a combination of the two agents in a form as instantly recited in amended claim 5. But Jensen discloses that even though such a combination may have a clear effect only when it is used for treating a tumor that is situated within the CNS it can also be beneficial in other settings too. If the tumor is situated in the peritoneal cavity the topoisomerase poison could be administered locally and the other

component can be administered via i.v. (col. 5, lines 27-44), Jensen also teaches that the active agents an be administered in conventional forms including tablet form (orally administrable form; col. 4, lines 19-23). The treatment schedules could also vary (col. 9, lines 5 through 31). This means that the active agents are administered in a form that is suitable depending on the location of the tumor.

Palepu et al teach the use of piperidinedione (abbreviated as ADR-529 and also known as ICRF-187) is a cardio protective agent used in antitumor therapy and in addition to being a cardio protective agent also acts as a sensitizer to ionizing radiation (col. 1, lines 27-36).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a topoisomerase II poison like etoposide and a dioxypiperazine like dexrazoxane in a form as instantly claimed since the use of a combination of the topoisomerase poison and a dioxypiperazine for the claimed forms individually is taught in the prior art and the use of radiation in tumor/cancer treatment is also well known.

One of skill in the art would be motivated to make the active agents in the form as instantly claimed since the active agents are administered in a form that is suitable depending on the location of the tumor, as taught by Jensen. Hence having the two agents in an infusible form and an orally administrable form would make it convenient and readily available for the desired mode of administration. Also having the active agent in an orally administrable form like a tablet is more convenient since it can be taken by the patient. This would avoid the additional step of setting up the instrumentation for i.v. administration and could also thereby reduce the cost.

Conclusion

Claims 1-10 are rejected

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathy Krishnan whose telephone number is 571-272-0654. The examiner can normally be reached on 8.30am-5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Ganapathy Krishnan/

Examiner, Art Unit 1623

/Shaojia Anna Jiang/

Supervisory Patent Examiner, Art Unit 1623